

Health and Environmental Effects
Profile for Dimethoate

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FOR DIMETHOATE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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TABLE OF CONTENTS

	<u>Page</u>
1. INTRODUCTION.	1
1.1. STRUCTURE AND CAS NUMBER	1
1.2. PHYSICAL AND CHEMICAL PROPERTIES	1
1.3. PRODUCTION DATA.	2
1.4. USE DATA	2
2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES.	3
3. EXPOSURE.	7
4. PHARMACOKINETICS.	9
4.1. ABSORPTION	9
4.2. DISTRIBUTION	9
4.3. METABOLISM	10
4.4. EXCRETION.	12
5. EFFECTS	13
5.1. CARCINOGENICITY.	13
5.2. MUTAGENICITY	15
5.3. TERATOGENICITY	21
5.4. OTHER REPRODUCTIVE EFFECTS	21
5.5. CHRONIC AND SUBCHRONIC TOXICITY.	22
5.6. OTHER RELEVANT INFORMATION	24
6. AQUATIC TOXICITY.	27
6.1. ACUTE TOXICITY	27
6.2. CHRONIC EFFECTS.	30
6.3. PLANT EFFECTS.	30
6.4. RESIDUES	30
6.5. OTHER RELEVANT INFORMATION	31
7. EXISTING GUIDELINES AND STANDARDS	33
7.1. HUMAN.	33
7.2. AQUATIC.	33
8. RISK ASSESSMENT	34
9. REFERENCES.	36
APPENDIX: LITERATURE SEARCHED.	51

LIST OF TABLES

<u>No.</u>	<u>Title</u>	<u>Page</u>
5-1	Mutagenicity of Dimethoate.	16
5-2	Acute Toxicity of Dimethoate.	25
6-1	Acute Lethal Effects of Dimethoate to Freshwater Fish . . .	28
6-2	Acute Median Lethal Effects of Dimethoate to Other Aquatic Organisms	29

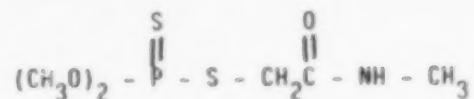
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
DNA	Deoxyribonucleic acid
EC ₅₀	Median effective concentration
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	Intravenous
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
s.c.	Subcutaneous
SCE	Sister chromatid exchange
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Dimethoate is the common name for O,O-dimethyl S-(N-methylcarbamoylmethyl)-phosphorodithioate. It is also known as Cygon, Fosfamid, Dimetate, Rogor and a host of other synonyms (NIOSH, 1983). The structure of dimethoate is given below (Melnikov, 1971):



Molecular formula: $\text{C}_5\text{H}_{12}\text{NO}_3\text{PS}_2$

Molecular weight: 229.2

The Chemical Abstracts Services (CAS) Registry Number for dimethoate is 60-51-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Dimethoate is a white, crystalline solid at ambient conditions, with a camphor-like odor (BCPC, 1977). Dimethoate is thermally unstable, undergoes oxidation in air, and readily hydrolyzes in alkaline media (Melnikov, 1971). Some of its physical and chemical properties are given below:

Melting point:	51-52°C (BCPC, 1977)
Boiling point:	107°C at 0.05 mm Hg (Melnikov, 1971)
Density:	1.281 at 50°C (BCPC, 1977)
Vapor pressure:	8.5×10^{-6} mm Hg at 20°C (Melnikov, 1971)
Volatility:	0.107 mg/m ³ (Melnikov, 1971)
Water solubility at 21°C:	25 g/l (BCPC, 1977)
Log octanol/water partition coefficient:	2.71 (Verschuere, 1983)

1.3. PRODUCTION DATA

Dimethoate was produced in 1981 by American Cyanamid, Linden, New Jersey (SRI, 1982). The most recent production data available indicate that 2.5 million pounds of dimethoate were produced in 1976 (U.S. EPA, 1979). American Cyanamid may have domestic production facilities for dimethoate, but they did not appear to produce it domestically in 1982 (SRI, 1983).

Dimethoate may be produced by reacting sodium 0,0-dimethyl phosphorodithioate with 2-chloro-N-methylacetamide; by reacting 0,0-dimethyl phosphorodithioate with phenyl chloroacetate and treating the product with methylamine; or by reacting methylamine with methyl(dimethoxyphosphinothioylthio)acetate (BCPC, 1977). The compound is usually marketed as a 40% emulsifiable concentrate (Melnikov, 1971).

1.4. USE DATA

Dimethoate is an organophosphate contact and systemic insecticide and acaricide used to control a broad spectrum of insects and mites. The U.S. EPA has cancelled the registration of dimethoate dust formulations and prohibits its application without the use of personal protective equipment (Federal Register, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Dimethoate is a thermally unstable molecule, rapidly decomposing to a more toxic acetylcholinesterase inhibitor. Impurities in dimethoate or storage in iron or steel containers may catalyze its decomposition. The compound is more stable when dissolved in organic solvents (Melnikov, 1971).

The fate of dimethoate in soil has been reported by several investigators. Although usually not directly applied to soil, dimethoate may enter soil from overspray and rainfall runoff (Duff and Menzer, 1973). El Beit et al. (1977, 1978) studied the loss of dimethoate from a variety of soils. Evaporation from soil columns was dependent on the depth of incorporation and the type of soil. The average loss of dimethoate in 6 days caused by evaporation from uncovered soil columns was 40.4, 32.3, 23.0 and 24.9% in sand, sandy clay loam, loam and clay loam, respectively. Leaching losses of dimethoate were observed to be dependent on the applied concentration and soil type. Soil columns containing clay, clay loam, loam, sandy clay loam and sand were leached with the equivalent of 2.5 cm of rain; average dimethoate losses for a range of starting concentrations (2, 5, 10, 30, 54, 74 $\mu\text{g}/\text{column}$) were 39.6, 44.7, 66.9, 69.3 and 78.6%, respectively (El Beit et al., 1977). The effect of soil treatment with urea and $\text{Ca}(\text{OH})_2$ (lime) on dimethoate leaching was reported by El Beit et al. (1978). A 14-day perfusion flask experiment in water, lime or urea-treated soil resulted in dimethoate losses from leaching of 79.2, 83.0 or 72.3%, respectively. Bohn (1964), however, reported the absence of dimethoate migration below 3 inches in field treated sandy loam soil. The soil was treated with 1 pound dimethoate/acre up to 3 times and analyzed for dimethoate up to 14 days after application. Soil half-life during drought and moderate rainfall conditions were -4 and -2.5 days, respectively. Duff and Menzer (1973)

reported that the downward movement of dimethoate in the field was somewhat dependent on soil type and was increased with increasing soil moisture content. This supported the work of Graham-Bryce (1969) who observed that the diffusion of dimethoate in a silt loam soil was increased over an increasing range of soil moisture content. Diffusion was found to occur predominantly in the liquid phase as opposed to the vapor phase. This may not represent an extremely effective transport process, however, as it was estimated that dimethoate could move ~2.5 cm in 1 month in soil containing 42.9% moisture; the movement thereafter decreases over time.

In moist soils, dimethoate is readily oxidized to the more toxic compound, dimethoxon (Duff and Menzer, 1973). The role of microbial degradation in the removal of dimethoate from the environment is uncertain, but it is believed to be less important than chemical degradation. Dimethoate degraded faster in 2-week incubations in nonsterile soil (77%) than in gamma-irradiated (20%) or heat sterilized soil (18%); microbial degradation was presumed (Getzin and Rosefield, 1968). El Beit et al. (1977) reported that dimethoate can be degraded chemically or by soil biota. Samples of autoclaved sand, sandy clay loam, loam and clay loam soils incubated with dimethoate (30 days) had more insecticide loss than similarly treated nonsterile soils. In clay soil, however, degradation of dimethoate was observed to be greater in nonsterile than in sterile samples. The nonsterile soils were observed to contain the microorganisms Actinomycetes, gram negative and gram positive bacilli, yeasts, Penicillium, Aspergillus and algae. The authors speculated that autoclaving may have destroyed some of the soil organic matter, allowing for more complete recovery of the dimethoate. Rosenberg and Alexander (1979) reported that bacterial cultures isolated from soil and sewage (Pseudomonads) grew on dimethoate, but only in the presence of another phosphorus source.

Dimethoate is rapidly oxidized in and on plants. Depending on the dosage, it is usually degraded on plants within 10-20 days (Melnikov, 1971). Dauterman et al. (1960) reported that dimethoate was oxidized to dimethoxon in potato, cotton, corn and pea plants by enzymatic and nonenzymatic processes. Lucier and Menzer (1968) studied the metabolism of radiolabeled (carbonyl- ^{14}C and ^{32}P) dimethoate in bean plants. When applied to the surface of leaves, 6 and 13 isolatable metabolites were observed from the ^{14}C - and ^{32}P -dimethoate compounds, respectively.

Few data regarding the fate of dimethoate in the atmosphere were located in the available literature. Dauterman et al. (1960) reported that large losses of dimethoate due to volatilization from treated cotton leaves. Fifty-eight percent of the dimethoate applied to leaves was lost after 10 days, with no substantial loss thereafter. El Beit et al. (1977) reported that evaporative losses from soils averaged 40, 32, 23 and 25% for sand, sandy clay loam, loam and clay, respectively, over a 6-day period. In addition, the authors found that dimethoate losses were directly proportional to water losses. Dimethoate may be hydrolyzed and chemically oxidized in the atmosphere, as such nonenzymatic reactions have been reported to occur on an untreated glass surface left in a greenhouse. Hydrolysis and oxidation products accounted for 11 and 1.5% of the applied dimethoate after 7 days (Dauterman et al., 1960).

The fate of dimethoate in water has been investigated under laboratory and environmental conditions. Relatively little leaching of dimethoate was observed in a field trial (Bohn, 1964), but moderate leaching has been observed in soil columns (El Beit et al., 1977, 1978). Irrigation and rainfall runoff is a potential source of aquatic dimethoate contamination, since residues of the insecticide were repeatedly detected in cornfield tailwater pits (Kadoun and Mock, 1978).

Dimethoate is rapidly hydrolyzed in alkaline solution, forming a variety of products. The time required for 50% hydrolysis (70°C) at pH 9 and pH 2 is 0.8 and 21 hours, respectively (Melnikov, 1971). The hydrolysis half-life of dimethoate in ethanol:pH 6.0 buffer solution (20:80) at 70°C was 12 hours (Ruzika et al., 1967). The half-life of dimethoate by hydrolysis at 70°C in Thames River water and Irthing River water (20% ethanol present) was reported to be 22 and 18 hours, respectively. At the lower temperatures encountered in natural systems, however, the hydrolysis rates are expected to be several hundred times slower (Ruzika et al., 1967).

Eichelberger and Lichtenberg (1971) studied the persistence of dimethoate in samples of raw river water from the Little Miami River. Samples of water (pH 7.3-8.0) were contaminated with 10 µg dimethoate/l, and allowed to incubate at room temperature for 8 weeks. The dimethoate concentration after 1 hour, 1 week, 2 weeks, 4 weeks and 8 weeks was 10, 10, 8.5, 7.5 and 5.0 µg/l, respectively. Environmental conditions may cause the actual rates of such degradation to vary.

3. EXPOSURE

STORET contains no monitoring data for dimethoate; however, the available literature provided data regarding the measurement of dimethoate in drinking water, crop residues and in the air and on the skin of agricultural insecticide applicators. Maddy et al. (1982) monitored the water from 54 wells in California, in an area where dimethoate was used for at least 15 years. The compound was not detected (detection limit <5.0 ppb) in well water. LaBel et al. (1979) analyzed 130 L of Ottawa tap water for dimethoate and could not detect the compound. The detection limit was <1 ng/L. Kadoum and Mock (1978) reported detecting dimethoate in 11/11 tailwater pits serving cornfields in Kansas. Tailwater is consumed by several species of wildlife including pheasants, doves, rabbits, coyotes, deer and waterfowl. The mean concentration of dimethoate was 1.9 ppb.

Wolfe et al. (1967) estimated the potential dermal and respiratory exposure to pesticide applicators. An applicator using a high pressure power hand gun to apply the compound had mean dermal and respiratory exposure of 420 and 0.2 mg/hour, respectively. A tractor driver (presumably) pulling the high pressure compressor had mean dermal and respiratory exposure of 3.1 and 0.1 mg/hour, respectively. Copplestone et al. (1976) estimated the dimethoate exposure to pesticide spray applicators in the Sudan. Respiratory exposures ranged from 5.1-19.9 µg/day. Mean dermal exposures (µg dimethoate on a 25 cm² cellulose pads placed on the skin) ranged from 25.55 µg/25 cm² on the lower leg to 0.11 µg/25 cm² on the upper abdomen. No significant differences were observed in pre- and postspray blood cholinesterase levels.

Carman et al. (1982) estimated dimethoate exposure to tractor drivers spraying citrus trees with air blast and oscillating boom methods. Air samples collected from the breathing zone of applicators contained mean values of 4-93 μg dimethoate/ m^3 and 2-64 μg dimethoate/ m^3 for the oscillating boom and air blast application method, respectively.

The occupational dimethoate exposure to pesticide applicators, mixers, loaders, pilots, flaggers and other agricultural users has been estimated by the U.S. EPA (Federal Register, 1981). Exposures ranged from 0.00005-0.39 mg/kg/day for combined dermal and inhalation exposure.

4. PHARMACOKINETICS

4.1. ABSORPTION

Brady and Arthur (1963) administered [^{32} P]dimethoate to groups of four rats of mixed sex (strain not specified) either by dermal (100 mg/kg bw) application or by oral gavage (50 mg/kg bw). Dimethoate was apparently absorbed following both routes of administration. Absorption of orally administered dimethoate was possibly somewhat more efficient than that of the dermally applied material, as judged by the relative excretion of radioactivity (vide infra); however, quantitative estimates of absorption were not made.

Shah and Guthrie (1973) investigated the ability of dimethoate to penetrate isolated sections of the mouse gastrointestinal tract. They found that dimethoate rapidly penetrated the tissues of the small intestine, colon and rectum, with the highest rates of penetration occurring in the colon and rectum. The age of the mice had insignificant effects on the extent of penetration.

Carman et al. (1982) found that agricultural workers involved in applying dimethoate using either oscillating boom or airblast units were exposed both dermally and by inhalation. Analysis of urine for dialkylphosphate residues indicated that significant amounts had been absorbed; however, no estimate of the relative importance of the two routes of exposure was made.

4.2. DISTRIBUTION

Only limited information is available on the tissue distribution of dimethoate. In an abstract of a Russian article, Fedorenko et al. (1981) reported residue levels in the tissues of forest animals (species unspecified) following aerial spraying with 38% dimethoate. Animal tissues contained higher concentrations of dimethoate than did soil, water or plants.

The tissues containing the highest concentrations were brain and, initially, lung, implying that inhalation may be a major route of exposure under these conditions.

4.3. METABOLISM

Dimethoate appears to be metabolized extensively by mammals. Thus, Brady and Arthur (1963) found that >95% of the radioactivity recovered in the urine and feces of rats treated with [^{32} P]dimethoate was in the form of hydrolytic products, based on chloroform/water partition coefficients.

Uchida and O'Brien (1967) observed the degradation of dimethoate by human liver slices. The necessity of freezing the liver tissue before use may have affected the quantitative results; however, conclusions should still be valid on a qualitative level. The major product observed was dimethoate acid $[(CH_3O)_2P(S)SCH_2COOH]$, the sole product of amidase action. O,O-Dimethyl phosphorodithioate $[(CH_3O)_2P(S)SH]$ was also identified. Several other metabolites, presumably phosphatase products, were detected but not identified. O-De-methylation did not appear to occur to an appreciable extent.

Uchida et al. (1966) compared the relative roles of the amidase and phosphatase pathways in the in vitro degradation of dimethoate by liver from female mice, male guinea pigs and female guinea pigs. Livers from female mice degraded dimethoate ~50% by amidase; however, in female guinea pigs, hepatic amidase activity accounted for only 28% of the observed degradation. No amidase activity was detected in livers obtained from male guinea pigs. The synergism between EPN and dimethoate was demonstrated to be due to inhibition of both amidase and phosphatase, though amidase was more strongly affected.

Hassan et al. (1969) investigated the metabolism of i.p. administered (30 mg/kg bw) dimethoate by albino rats (strains unspecified) of both sexes in vivo and in vitro, using either [^{32} P] or [^{14} C]dimethoate. Oxidation to the more toxic dimethoxon was assumed to occur in vivo; however, no dimethoxon was detected in the urine or feces of rats treated with dimethoate. The recovered radioactive metabolites following administration of [^{32} P]dimethoate were identified as monomethylphosphate (5%), dimethylphosphate (18%), thiophosphoric acid (4%), dimethoate carboxylic acid (32%), dimethylphosphorothioic acid (30%), monomethylphosphate (1%), dimethylphosphate (3%) and dimethylphosphorodithioic acid (7%). Following administration of dimethoate labeled with ^{14} C in the methoxy groups, the observed urinary metabolites were monomethylphosphate (4%), dimethylphosphate (30%), dimethoate carboxylic acid (38%), dimethylphosphorothioic acid (21%), traces of mono- and dimethylphosphates (2%) and dimethylphosphorodithioic acid (5%). Methylamine liberated by these pathways is oxidatively demethylated to CO₂ and formate. Approximately 80% of the nonphosphorus moiety liberated by the action of esterases on the S-C bond are excreted in the urine as glucuronide conjugates.

Kaplanis et al. (1959) investigated the metabolism of 10 mg [^{32} P]dimethoate/kg bw in young Hereford bulls or steers following oral or i.m. administration. The major metabolic products were dimethyl phosphate and dimethyl phosphorothioate, along with several unidentified metabolites.

The metabolism of [^{32} P]dimethoate (10-40 mg/kg bw) following oral and i.m. administration has also been investigated in sheep (Chamberlain et al., 1961). The identified urinary metabolites were dimethyl phosphoric acid (50.55%), dimethyl phosphorothioic acid (7.68%), dimethyl phosphorodithioic

acid (0.41%), a carboxy derivative (4.26%) and parent compound (1.7%). Six unidentified metabolites were detected, ranging from 2.1-18.61% of the total metabolites.

Similar results were obtained in mice (Krueger et al., 1960) and rats (Lucier and Menzer, 1970). These later studies demonstrated oxidative desulfuration, resulting in the formation of P=O derivatives (the oxygen analog of dimethoate and its des-N-methyl derivative), which are believed to be the compounds responsible for most of dimethoate's toxicity.

4.4. EXCRETION

Chamberlain et al. (1961) found that within 72 hours after dosing, 80-90% of the administered radioactivity was found in the urine of sheep given [³²P]dimethoate. Amounts recovered in the feces ranged from 0.9-2.4%.

In cattle, 87-90% of the administered dose of dimethoate, as measured by ³²P, was excreted in the urine within 24 hours following an oral dose or 9 hours following an i.m. injection (Kaplanis et al., 1959). Less than 5% of the oral dose and ~1.1% of the i.m. dose were eliminated in the feces.

Excretion in the rat follows the same general pattern (Hassan et al., 1969; Brady and Arthur, 1963). Hassan et al. (1969) reported that 60% of the administered ¹⁴C was recovered in the urine and expired air of rats receiving [methoxy-¹⁴C]dimethoate, i.p. The relative amounts excreted by each route were not given. Brady and Arthur (1963) reported that 45 and 30.6% of the administered ³²P was excreted in the urine and 5.8 and 6.5% in the feces, respectively, following oral or dermal exposure to [³²P]dimethoate.

5. EFFECTS

5.1. CARCINOGENICITY

Three studies have been performed that bear directly on the carcinogenic potential of dimethoate (Gibel et al., 1973; NCI, 1977; Lewerenz et al., 1970). American Cyanamid and Montedison submitted the unpublished study by Lewerenz et al. (1970) in response to a U.S. EPA Rebuttable Presumption Against Registration (RPAR) notice (U.S. EPA, 1979). The details of the study are lacking, which severely limits the conclusions that can be drawn from it. Wistar rats were fed diets that resulted in a calculated exposure of 5.5 mg/kg/day for males and 5.88 mg/kg/day for females in the highest dose group (75 ppm in the diet). The number of groups, number of animals/group or the types of controls used were not included in the available data. The study was reported as negative for carcinogenesis; however, none of the pathology data were available for review.

Gibel et al. (1973) studied the carcinogenic potential of dimethoate in Wistar rats of both sexes (40 rats/group) following oral or i.m. administration or in AB mice (19 mice/group) following dermal application. Rats were treated twice weekly by gavage with 5, 15 or 30 mg/kg, or i.m. with 15 mg/kg. Doses of 30 mg/kg orally and 15 mg/kg i.m. resulted in statistically significant increases in the combined incidence of malignant tumors. Malignant tumors were found in 4/20 rats that received 30 mg/kg orally. These tumors consisted of one liver sarcoma, one malignant reticulosis and two sarcomas of the spleen. An i.m. dose of 15 mg/kg bw resulted in the production of one sarcoma of the spleen, one soft tissue sarcoma, one ovarian sarcoma, one reticulum cell sarcoma, one spleen sarcoma and one liver sarcoma, for a combined incidence of 6/30. The incidences of malignant

tumors in the oral and i.m. control groups were 0/36 and 0/35, respectively. The only other statistically significant result was a positive dose-related linear trend ($p < 0.01$) for orally administered dimethoate. Symptoms resembling human myeloproliferative syndrome (necrosis and cirrhosis of the liver, leukocytosis and hyperplasia of the blood-building parenchyma of the bone marrow and spleen) were also observed. Five of 19 mice developed malignant tumors (4 leukoses and 1 breast carcinoma). Only fibroadenoma of the breast was reported in the control animals. Although the incidence of malignant tumors at all sites was significant in the Gibel et al. (1973) study, the absence of a positive response at any one site or type makes the evidence for carcinogenicity only weakly suggestive.

The best available carcinogenicity data are from the National Cancer Institute bioassay (NCI, 1977). Dimethoate was administered in the diet to Osborne-Mendel rats (50 of each sex/group) and B6C3F₁ mice (50 of each sex/group). Matched controls consisted of 10 animals of each sex/dose group.

Initially, the low-dose diet contained 250 ppm dimethoate and the high-dose diet contained 500 ppm dimethoate (technical grade) for both the rats and mice. These doses were continued throughout the 80-week treatment period for female mice or 60- to 69-week treatment period for male mice; however, the doses for rats were reduced by a factor of 2 after 19 weeks for the males and 43 weeks for the females because of toxicity problems. Both male and female rats received dimethoate for a total of 80 weeks. The TWA doses for the low- and high-dose groups were 155 and 310 ppm for the male rats and 192 and 384 ppm for the female rats, respectively. The total time on study (treatment and observation) was 93-94 weeks for mice and 113-115 weeks for rats. There were no significant increases in tumor incidence in either sex of either species tested.

In conclusion, the animals evidence for the carcinogenicity of dimethoate is inadequate, using the criteria of the International Agency for Research on Cancer (IARC-Supplement 4).

5.2. MUTAGENICITY

The mutagenicity of dimethoate is summarized in Table 5-1. Ashwood-Smith et al. (1972) tested a large number of pesticides and biocides for possible mutagenic activity in an Escherichia coli WP2 try⁻ system. They reported dimethoate to be nonmutagenic under these conditions, but did not present the data on which this conclusion was based.

Fahrig (1973) tested dimethoate in a Saccharomyces cerevisiae system at seven dose levels over the range of 40-100 mM. A positive dose-response curve for the induction of mitotic gene conversions was observed. Dimethoate was intermediate between dichlorvos and bidrin in mutagenic potency.

Mohn (1973) retested dimethoate at five doses ranging from 1-6 mM in an E. coli system using induction of 5-methyltryptophan (5-MT) resistance as the measured endpoint. Under these conditions, dimethoate was mutagenic with a potency similar to that of bidrin, but less than dichlorvos and much less than N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), a known powerful mutagen.

Hanna and Dyer (1975) tested dimethoate (5-10 µl) in Salmonella typhimurium strains his C117, his G46, TA1530 and TA1535, and E. coli strains WP2, WP2 uvrA, CM561, CM571, CM611, WP67 and WP12. Only negative results were obtained in the S. typhimurium assays. Positive results were obtained in E. coli strains WP2 uvr and WP67 if the tester plates were incubated for 72 hours rather than the standard 48 hours.

Shirasu et al. (1976) tested dimethoate using 20 µl of a 1 mg/ml solution/plate in the Bacillus subtilis rec-assay using strains H17 Rec⁺

TABLE 5-1
Mutagenicity of Dimethoate

Species	Strain	Assay	Activation System	Concentration or Dose	Results	Comments	Reference
<i>E. coli</i>	WP2 try ⁻	reversion	-	NR	-	NC	Ashwood-Smith et al., 1972
<i>E. coli</i>	K-12	5-MT resistance	-	1-6 mM	-	NC	Mohn, 1973
<i>E. coli</i>	WP2, WP2 uvrA, CW61, CW571, CW611, WP67, WP12	reversion	-	5-10 μ M	+	Positive results in strains WP2 uvrA and WP67 only	Hanna and Dyer, 1975
<i>E. coli</i>	B/r try WP2, WP2 try hcr	reversion	-	20 μ M of a 1 mg/ml solution/plate	-	NC	Shirasu et al., 1976
<i>E. coli</i>	WP2 hcr	reversion	-	0-5000 μ g/plate	+	NC	Moriya et al., 1983
<i>S. typhimurium</i>	C117, his G46, TA1530, TA1535	reversion	-	5-10 μ M	-	NC	Hanna and Dyer, 1975
<i>S. typhimurium</i>	TA1535, TA1536, TA1537, TA1538	reversion	-	20 μ M of a 1 mg/ml solution/plate	-	NC	Shirasu et al., 1976
<i>S. typhimurium</i>	TA1535, TA100, TA1537, TA1538, TA98	reversion	-	0-5000 μ g/plate	+	Positive results in strain TA100 only	Moriya et al., 1983
<i>S. cerevisiae</i>	NR	mitotic gene conversion	-	40-100 mM	+	Intermediate in potency between dichlorvos and bldr in	Fährig, 1973
<i>S. pombe</i>	NR	forward mutation	+/-	NR	+	Mammalian microsomal preparation decreased the mutagenic potency of dimethoate.	Engraeve et al., 1980
<i>S. pombe</i>	NR	forward mutation	+/-	NR	-	Mouse liver S9 increased the toxicity of dimethoate to <i>S. pombe</i> .	Giloi-Delhalie et al., 1983
<i>B. subtilis</i>	H17rec ⁺ , M45rec ⁻	REC	-	20 μ M of a 1 mg/ml solution/plate	-	NC	Shirasu et al., 1976

TABLE 5-1 (cont.)

Species	Strain	Assay	Activation System	Concentration or Dose	Results	Comments	Reference
<i>P. mirabilis</i>	rec ⁺ hcr ⁺ , rec ⁻ , rec ⁻ hcr ⁻	differential toxicity	-	10 mg/plate	+	NC	Adler et al., 1976
Human	Lymphoid cells (LA2-007)	SCE	+/-	0.02-20 µg/ml	+	Positive results at concentrations of 2 or 20 µg/ml. No consistent effect of rat liver S9-mix.	Sobitt et al., 1982
Human	VA 4 cells	unscheduled DNA synthesis	+/-	10-1000 µM	+	Positive results with activation by rat liver S9.	Ahmed et al., 1977
Chinese hamster	V79 cells	SCE induction	+/-	10-80 µg/ml	+	A dose-related increase in SCE's was observed, both with and without activation by S9 mix.	Chen et al., 1981, 1982
Rat	Hepatocyte	unscheduled DNA synthesis	NA	500 µMol/ml	-	NC	Probst et al., 1981
Mouse	ICR	micronucleus	NA	100 mg/kg bw	-	Coadministered orally with 150 mg/kg bw of NaNO ₂	Seller, 1977
Mouse	Q	dominant lethal	NA	10 mg/kg bw or 0.093 mg/kg/day for 7 weeks	-	NC	Degraeve et al., 1978, 1982, 1979, 1983
Mouse	AB Jena-Halle, DBA, C57BL	<i>in vivo</i> cytogenetics dominant lethal	NA	60 mg/kg bw	+	NC	Mehez et al., 1982
Mouse	Swiss	micronucleus	NA	51.7 mg/kg	+	NC	Rani et al., 1980

NA = Not applicable; NC = no comment; NR = not reported

and M45 Rec⁻, and in reversion assays using E. coli strains B/r try WP2 and WP2 try hcr, and S. typhimurium strains TA1535, TA1536, TA1537 and TA1538. Negative results were obtained in all strains with dimethoate.

Seller (1977) converted dimethoate to the N-nitroso derivative, dissolved it in dimethyl sulfoxide (concentration not given) and tested 1, 10 or 100 µl of the resulting solution in S. typhimurium his G46. A positive dose-response relationship in the number of revertants/plate was noted. Dimethoate (100 mg/kg) plus NaNO₂ (150 mg/kg) was then tested by oral administration in the micronucleus assay using ICR mice and Chinese hamsters. The sodium nitrate was added so that dimethoate would be nitrated in vivo. Negative results were obtained in this test.

Degraeve et al. (1980) tested dimethoate for mutagenic activity in the yeast, Schizosaccharomyces pombe, both with and without activation by a mammalian microsomal preparation. Dimethoate was not mutagenic in this assay, either with or without activation.

Moriya et al. (1983) tested dimethoate, at doses ranging from 0-5000 µg/plate, for mutagenicity in E. coli strain WP2 hcr and S. typhimurium strains TA1535, TA100, TA1537, TA1538 and TA98. Positive results were obtained in strains WP2 hcr and TA100.

Gilot-Delhalle et al. (1983) obtained negative results in an S. pombe system, both with and without activation by a mouse liver S9 preparation. The S9 fraction increased the toxicity of dimethoate to S. pombe by 60%; however, no effects on mutagenicity were noted.

On the basis of these tests, dimethoate should be considered a weak mutagen in bacterial systems.

Adler et al. (1976) investigated the comparative ability of dimethoate to inhibit the growth of repair-proficient (rec⁺ hcr⁺) and repair-

deficient (rec^- and $rec^- hcr^-$) strains of Proteus mirabilis. Dimethoate (10 mg in 0.1 ml ethanol/plate) resulted in a 41% increase in the size of the zone of inhibition when the $rec^+ hcr^+$ strain was compared with the $rec^- hcr^-$ strain, indicating that dimethoate treatment results in significant damage to cellular DNA.

Sobti et al. (1982) studied the effects of dimethoate (0.02, 0.2, 2.0 and 20 $\mu\text{g/ml}$) on human lymphoid cells (LAZ-007), with or without activation by a rat liver S9 preparation. Dimethoate produced a significant increase in SCE at doses of 2 (57%) or 20 (97%) $\mu\text{g/ml}$ in the absence of S9 activation. The authors concluded that, following S9 activation, "significant enhancement (1% level) in the frequency of SCEs was caused by 20 $\mu\text{g/ml}$ of activated diazinon, phosdrin and dimethoate"; however, the number of SCEs in this series of tests following S9 activation (11.52 ± 0.28) was comparable to the number of SCEs obtained in the absence of S9 activation in other test sequences (13.71). Activation by rat-liver S9 cannot, therefore, be considered to have a definite effect on dimethoate mutagenicity, based on the results of this test.

Chen et al. (1981, 1982) investigated the effect of 10, 20, 40 or 80 μg dimethoate/ml on Chinese hamster V79 cells. Treatment resulted in a dose-related increase in the number of SCEs, both with and without activation by S9 mix. No significant delay in the cell cycle was observed following dimethoate treatment at any dose level.

The ability of dimethoate to induce unscheduled DNA synthesis has been measured in SV-40 transformed human cells (VA-4) (Ahmed et al., 1977) and primary rat hepatocytes (Probst et al., 1981). Ahmed et al. (1977) tested dimethoate at concentrations of 10, 100 or 1000 μM , both in the presence

or absence of rat liver S9 preparations. Dimethoate produced negative results at all concentrations in the absence of S9 activation; however, at 100 and 1000 μ M, significant induction of unscheduled DNA synthesis was observed following activation by rat liver S9. Probst et al. (1981) obtained negative results in rat hepatocytes at a concentration of 500 nmoles/mL.

In a series of studies, Degraeve et al. (1978, 1979, 1982, 1983) investigated the mutagenicity of dimethoate in mammalian systems in vivo. Q (Edinburgh) strain mice were dosed with 10 mg dimethoate/kg i.p. or with 0.6 ppm in the drinking water, 5 days/week, for 7 weeks (0.093 mg/kg/day). Neither treatment resulted in an increase in pre- or postimplantation losses in the dominant lethal mutation assay or in the incidence of chromosome damage in bone marrow or spermatogonial cells.

Nehez et al. (1982), administering a dose of 60 mg dimethoate/kg i.p., found that the number of chromosome aberrations in bone marrow cells increased from 6/200 cells in controls to 63/200 cells in treated mice, 24 hours following treatment. Positive results were also obtained in the dominant-lethal test using AB Jena-Halle, DBA and CFLP mice.

Rani et al. (1980) tested dimethoate (51.7 or 155 mg/kg) in the micronucleus and host-mediated assays using Swiss albino male mice. Doses of 51.7 mg/kg in the micronucleus test or 155 mg/kg in the host-mediated assay produced a significant increase in the frequency of polychromatic erythrocytes with micronuclei and the number of S. typhimurium revertants, respectively.

5.3. TERATOGENICITY

Abstracts from the Russian and German literature indicate that dimethoate (dose not specified) is embryotoxic but not teratogenic in rats and mice

following i.p. administration (Iskhakov and Magrupova, 1976; Scheufler, 1975, 1976).

Khera et al. (1979) tested dimethoate (as Cygon 4E, 47.3% dimethoate, 52.7% unspecified ingredients) for teratogenicity in groups of 20 female Wistar rats. Three, 6, 12 or 24 mg Cygon 4E in corn oil/kg bw/day was administered by gavage on days 6-15 of gestation. The control group received corn oil only. The two highest doses produced a significant increase in the incidence of wavy ribs. No significant fetal toxicity was observed. A dose of 12 mg Cygon 4E/kg bw/day administered to cats on days 14-22 of gestation was associated with a high level (8/39 fetuses) of polydactyly (Khera, 1979). No control data were presented in this abstract.

5.4. OTHER REPRODUCTIVE EFFECTS

Budreau and Singh (1973) administered dimethoate (60 ppm in the drinking water) to five generations of CD-1 mice. Each generation consisted of 14 females and 10 males. This treatment resulted in reduced mating success and longer reproduction times. No histopathological changes were found that would account for the observed decrease in reproductive performance. No teratogenic potential was detected. Additional information regarding this study can be found in Section 5.5.

In an unpublished 3-generation study by American Cyanamid (1965), albino mice of the CF₁ strain were fed 0, 5, 15 or 50 ppm dimethoate in the diet. According to the authors, "reproduction and lactation performance was good for all groups." A few of the dams receiving 50 ppm had tremors, however, and an EPA scientist reviewed the data and concluded that there was an effect on litter survival at 50 ppm, although the effect was not statistically significant (U.S. EPA, 1979; Federal Register, 1977). Assuming that a

mouse consumes the equivalent of 13% of its body weight daily as food, the dosages of dimethoate corresponding to 15 and 50 ppm would be 2.0 and 6.5 mg/kg bw/day.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In a 5-generation chronic study, Budreau and Singh (1973) maintained groups of 14 female and 10 male CD-1 mice on 60 ppm dimethoate in the drinking water. The actual dosage of dimethoate was reported to be 9.5-10.5 mg/kg/day. This treatment had deleterious effects on reproductive performances (vide supra) and resulted in increased mortality of the pups during the first week after birth; however, no histopathological changes were observed in the ovaries, testes, liver or kidneys of treated rats. The unpublished American Cyanamid (1965) report of a 3-generation study with CD-1 mice indicates that a dietary level of 15 ppm dimethoate produced no effects and 50 ppm produced tremors and a slight effect on litter survival.

Sanderson and Edson (1964) administered dimethoate ("laboratory grade") to humans and to Wistar or Glaxo-Wistar rats. The human subjects (20 at 0.04 mg/kg/day, 1 at 0.13 mg/kg/day and 1 at 0.26 mg/kg/day) ingested dimethoate daily for 3-4 weeks. No overt toxic effects or blood cholinesterase inhibition were observed. In other studies, these authors maintained groups of 20 male rats on diets containing 0.5, 2, 2.5, 5, 10, 20, 40, 50, 200 or 800 ppm dimethoate for 6-12 months. The 800 ppm level produced severe signs of cholinergic toxicity and was discontinued. The 200 ppm level produced similar but less severe signs of toxicity. A dietary intake of ≤ 50 ppm resulted in no overt toxic effects; however, erythrocyte and plasma cholinesterase were inhibited in the group receiving diets containing 50 ppm dimethoate. No inhibition of cholinesterase was observed at dietary

concentrations of ≤ 10 ppm. No histopathologic effects were seen in any group. An additional experiment in rats was performed using i.p. injections (24 injections in 34 days). Cholinesterase inhibition occurred at doses >0.7 mg/kg/day, overt toxicity appeared at doses >3 mg/kg/day and some deaths occurred at doses >40 mg/kg/day.

Edson et al. (1967) conducted another study with humans, using a greater number of subjects and higher doses. Dimethoate was administered orally 5 days/week; the authors reported the daily dosage after adjusting by 5/7, to spread the dosage over the entire week. The number of subjects was 12 at 0.068 mg/kg/day for 28 days (duration of test), 9 at 0.202 mg/kg/day for 39 days, 8 at 0.434 mg/kg/day for 57 days, 6 at 0.587 mg/kg/day for 45 days and 6 at 1.02 mg/kg/day for 14 days. Whole blood cholinesterase activity and erythrocyte cholinesterase activity were inhibited (as compared with pretreatment levels) only at dosages ≥ 0.434 mg/kg/day. At 0.434 mg/kg, the downward trend in activity started at 20 days of treatment and continued to the end of the 57-day test period. At the two higher dosages, this effect was seen earlier and progressed more rapidly. Plasma cholinesterase activity was also measured, but not reported. No localized gastrointestinal effects or any other signs of toxicity were noted.

In the NCI (1977) carcinogenicity bioassay, rats were maintained on diets containing dimethoate at 155 or 310 ppm (males) and 192 or 384 ppm (females) for 80 weeks (see Section 5.1. for details of dosing schedule). Mice were maintained on diets containing 250 or 500 ppm dimethoate for 60-69 weeks (males) or 8 weeks (females). During the first 2 weeks of the study, high-dose rats evidenced typical symptoms of organophosphate intoxication, including hyperexcitability, tremors and convulsions in response to acoustic

stimuli, decreased food consumption and depression of body weight. Tremors were noted in both low- and high-dose mice starting at week 16 or later but usually not persisting for more than a few weeks. In rats, survival appeared to be decreased in a dose-related manner among low- and high-dose females, but in males, the survival of controls was unusually low (i.e., lower than in any dosed group of male or female rats). Survival among high-dose males was decreased relative to survival in low-dose males. Survival in mice was unaffected. No clear indication of an association between nonneoplastic histopathologic lesions and treatment was observed in either species.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of dimethoate is summarized in Table 5-2. The technical and laboratory grade products are as toxic as, and often more toxic than, the pure compound. These data imply that dimethoate often contains an impurity that is more toxic than, or acts synergistically with, dimethoate.

Curtes et al. (1981) reported a case of late peripheral neuropathy that was apparently due to voluntary ingestion of dimethoate. Lotti et al. (1981) criticized the Curtes et al. (1981) report because the active ingredient involved was insufficiently characterized. In addition, they found no inhibition of neurotoxic esterase in brain autopsy material from hens or a fatal human poisoning. This would make a late peripheral neuropathy following acute intoxication with dimethoate seem unlikely; however, the possibility cannot be excluded without further study.

Several investigators have studied the effects of exposure to organophosphate insecticides, including dimethoate, on agricultural and production workers (Areekul et al., 1981; Kraus et al., 1981a,b). In the absence of

TABLE 5-2
Acute Toxicity of Dimethoate^a

Species/Sex	Purity	Route	LD ₅₀ (mg/kg)
Rat/male	pure	oral	500-600
Rat/female	pure	oral	570-680
Rat/male	laboratory grade	oral	280-350
Rat/female	laboratory grade	oral	300-356
Rat/male	technical	oral	180-325
Rat/female	technical	oral	240-336
Rat/male	laboratory grade	i.p.	175-325
Rat/female	laboratory grade	i.p.	350
Rat/male	laboratory grade	s.c.	350
Rat/male	laboratory grade	i.v.	450
Mouse/female	pure	oral	60
Mouse/female	technical	oral	60
Mouse/female ^b	96%	i.p.	300
Mouse	laboratory grade	s.c.	120
Mouse	technical	s.c.	60
Hamster/male	technical	s.c.	60
Hamster/male	laboratory grade	s.c.	200
	laboratory grade	oral	200
Rabbit	pure	oral	500
Rabbit	laboratory grade	oral	450
Rabbit	technical	oral	300
Guinea pig	technical	oral	350-400
Guinea pig	laboratory grade	oral	600
Guinea pig	pure	oral	550

^aSource: Sanderson and Edson, 1964 (unless otherwise specified)

^bSource: Sterri et al., 1979

quantitative exposure data, it is not possible to draw many conclusions from these studies. With the exception of decreased serum cholinesterase activity, no effects were observed in the exposed workers.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethal effects of dimethoate have been determined in several species of freshwater fish (Table 6-1). Species of fish not common to the United States, Channa gachua and Saccobranchus fossilis, appeared most sensitive, having 96-hour LC_{50} values of 4.48 and 4.57 mg dimethoate/l, respectively (Verma et al., 1978, 1982). The bluegill sunfish had a 96-hour LC_{50} of 6.0 mg/l (FWS, 1965). The rainbow trout would be expected to be more sensitive than the bluegill, but the trout was exposed only to Rogor 40, a 32% mixture of dimethoate (Alabaster, 1969). Based on bioassays of dimethoate in Channa gachua, a relatively sensitive species, Verma et al. (1978) suggested that 1.3733 mg/l was a safe concentration.

The acute toxicity of dimethoate on embryolarval stages of fish has been examined (Roales and Perlmutter, 1974; Baba et al., 1977). The 48- and 72-hour LC_{50} values for dimethoate in zebrafish embryos, Brachydanio rerio, were 940 and 259 mg/l, respectively. Baba et al. (1977) reported that dimethoate caused a high incidence of vertebral deformation in exposed yellowtail, Seriola dorsalis.

The water flea, Daphnia magna, had a 48-hour LC_{50} value of 2.50 mg dimethoate/l (Table 6-2). Another freshwater crustacean, Gammarus lacustris, was more sensitive, with a 48-hour LC_{50} of 0.40 mg/l (USDI, 1968). Nymphs of the stonefly, Pteronarcys californica, were the most sensitive organism tested, having a 96-hour LC_{50} value of 0.043 mg/l (FWS, 1965; Sanders and Cope, 1968).

TABLE 6-1

Acute Lethal Effects of Dimethoate to Freshwater Fish

Species	Duration (hours)	LC ₅₀ (mg/l)	Method	Reference
Rainbow trout, <u>Salmo gairdneri</u>	24 48	58.0* 27.0*	NR NR	Alabaster, 1969
Bluegill sunfish, <u>Lepomis macrochirus</u>	24 48 96	28.0 9.6 6.0	NR NR NR	FWS, 1965 FWS, 1965; USDI, 1968 FWS, 1965
Carp, <u>Cyprinus carpio</u>	168	22.39	NR	Basak and Konar, 1978
Singhi, <u>Heteropneustes fossilis</u>	168	45.71	NR	Basak and Konar, 1978
Tilapia, <u>Tilapia mossambica</u>	168	23.77	NR	Basak and Konar, 1978
<u>Channa gachua</u>	24 48 96	5.16 4.96 4.48	static static static	Verma et al., 1978
<u>Channa punctatus</u>	96	20.5	NR	Anees, 1975
<u>Saccobranhus fossilis</u>	24 48 72 96	5.14 4.80 4.67 4.57	static-aerated static-aerated static-aerated static-aerated	Verma et al., 1982

*Testing was conducted on Rogor 40, contained 32% dimethoate.

NR = Not reported

TABLE 6-2

Acute Median Lethal Effects of Dimethoate to Other Aquatic Organisms

Species	Duration (hours)	LC ₅₀ (mg/l)	Method	Reference
Water flea, <u>Daphnia magna</u>	48	2.50	NR	USDI, 1968
Scud, <u>Gammarus lacustris</u>	48	0.40	NR	USDI, 1968
Stonefly nymph, <u>Pteronarcys californica</u>	24	0.51	NR	FWS, 1965; Sanders and Cope, 1968
	48	0.14	NR	FWS, 1965; Sanders and Cope, 1968
	96	0.043	NR	FWS, 1965; Sanders and Cope, 1968

NR = Not reported

6.2. CHRONIC EFFECTS

The effects of chronic exposure to Rogor (30% dimethoate) on the development of the Indian bullfrog, Rana tigerina, have been determined (Mohanty-Hejmadi and Dutta, 1981). A decrease (70% of controls) in the number of metamorphosed tadpoles was reported in tests where eggs were exposed to 3.0 µg Rogor/l. No eggs exposed to 10 mg/l metamorphosed. When limb bud stage tadpoles were exposed to 10 mg Rogor/l, only 20% failed to metamorphose but the time until metamorphosis was extended from 18 days (for controls) to 59 days. The time until metamorphosis was lengthened in exposed eggs and limb bud stage tadpoles at 1 mg Rogor/l (Mohanty-Hejmadi and Dutta, 1981).

6.3. PLANT EFFECTS

The 96-hour EC_{50} values of dimethoate for growth inhibition in the marine algae, Skeletonema costatum, as determined by decreased dry weight, protein content, cell count and carbohydrate and chlorophyll a content were 9.5, 10.65, 11.2 and 11.0 mg/l (Ibrahim, 1983). The 96-hour EC_{50} values for growth inhibition by dimethoate in Amphiprora paludosa, determined by the respective methods, were 12.5, 10.0, 10.5 and 10.8 mg/l. The unicellular alga, Phaedoactylum tricorutum, had similar 96-hour EC_{50} values of 6.85, 11.2, 8.5 and 10.2 mg/l, respectively.

6.4. RESIDUES

In a Russian study, dimethoate applied to a study pond at 1.5 kg/hectare was hydrolyzed within 30 days. Residues were detected in fish for 30 days after application. Residue accumulation occurred in the kidneys at levels as high as 159 mg/kg (Korzhevenko et al., 1977). Persistence of dimethoate added to river water at 0.01 mg/l was studied over an 8-hour period

(Eichelberger and Lichtenberg, 1971). Dimethoate concentrations were 100, 85, 75 and 50% of the original concentration after 1, 2, 4 and 8 weeks, respectively.

6.5. OTHER RELEVANT INFORMATION

Histological pathologies of the gills, including hyperplasia and necrotic lamellae, have been associated with dimethoate exposure in rainbow trout, Salmo gairdneri, carp, Cyprinus carpio, Idus idus and Channa gachua (Sigloch, 1981; Dalela et al., 1979). During the exposure periods, up to 32 days, bronchial damage increased in severity with time.

Hepatic damage following dimethoate exposure was reported in Channa punctatus. Hepatic vacuolization occurred by 24 hours and cytoplasmic granulation was extensive by 96 hours (Anees, 1978). Histopathologies of the intestine of treated C. punctatus were noted at 96 hours postexposure. Muscular layers showed slight degeneration, submucosa showed irregular cellularity and mucosal microvilli were vacuolated (Anees, 1976).

Increased hepatic and renal acid phosphatase and succinate dehydrogenase activity was reported in catfish, Heteropneustes fossilis, within 48 hours of exposure to dimethoate at sublethal concentrations (Dubale and Awasthi, 1982). In Channa gachua, dimethoate administered at 6.2 mg Rogor/l caused increased hepatic, renal and muscle and phosphatase activity. At 1.491 mg Rogor/l, enzyme activity was decreased (Dalela et al., 1978). Several studies have reported brain acetylcholinesterase inhibition following dimethoate treatment in fish (Verma et al., 1979; Fytizas and Vassiliou, 1980; Coppage, 1972). Decreased acetylcholinesterase activity was dose-related, and a significant difference ($p < 0.01$) from controls was evident at ~0.5 mg dimethoate/l and 0.8 mg Rogor/l (Fytizas and Vassiliou, 1980; Verma et al., 1979).

Rogor (containing ~35% dimethoate) at 1 mg/l induced distinctive changes in the hematologic profile of rainbow trout, including increased red blood cell count, hematocrit and hemoglobin concentration, and a decreased leukocyte count (Juelich, 1979). Hematologic changes became apparent 6 hours after exposure at 3.5 mg Rogor/l. Recovery of normal hematologic parameters following 96 hours of exposure at 5 mg/l was not complete within the 14-day recovery period.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

No TLV has been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 1980). Dimethoate is currently approved for use on food crops; however, the U.S. EPA has moved to deny registration for all dust formulations and to require the use of protective clothing and respirators during application (Federal Register, 1981). The U.S. EPA established tolerances for dimethoate, including its oxygen analog, in or on raw agricultural commodities ranging from 0.002 ppm in milk to 2.0 ppm in a variety of fresh fruits and vegetables (Code of Federal Regulations, 1982). The U.S. EPA (1983) reports an ADI of 0.0200 mg/kg/day, based on a NOEL for cholinesterase inhibition in humans of 0.200 mg dimethoate/kg/day (determined by "subchronic daily dosing") and a safety factor of 10. No other details were provided. This value is the same as the ADI derived by the World Health Organization (Vettorazzi, 1975) from the data of Sanderson and Edson (1964) and Edson et al. (1967) regarding cholinesterase inhibition in humans.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of dimethoate could not be located in the available literature.

8. RISK ASSESSMENT

The available data are insufficient to establish carcinogenic risk criteria, or even to state definitively that a carcinogenic risk exists. The EPA's Carcinogen Assessment Group (CAG) considers the evidence to be suggestive of a carcinogenic effect of dimethoate, but regards the data as inadequate for quantitative risk assessment (U.S. EPA, 1979; Federal Register, 1981). The International Agency for Research on Cancer (IARC) has not prepared a monograph on dimethoate. Positive results have been obtained in some assays of the potential mutagenicity and genotoxicity of dimethoate (see Section 5.2.).

Several long-term studies have been performed. The only chronic study available, the oral carcinogenicity study in rats and mice by the NCI (1977), does not provide a NOEL and NOAEL. The low dose (192 ppm dimethoate in the diet, corresponding to 9.6 mg/kg/day assuming that rats consume the equivalent of 5% of their body weight daily as food) may have produced a decrease in survival among female rats, although the data are equivocal. No histopathologic effects were seen. In a study of shorter duration, male rats fed 200 ppm dimethoate in the diet for 6 months had cholinergic effects (Sanderson and Edson, 1964). A dietary level of 50 ppm (~2.5 mg/kg/day) for 6-12 months was a NOAEL for male rats in this study; no overt signs of toxicity or histopathologic effects were observed, although plasma and erythrocyte cholinesterase activities were inhibited (Sanderson and Edson, 1964). The results of two multigeneration reproductive studies indicate that, for mice, ingestion of ~2 mg/kg/day is a NOAEL, ~6.5 mg/kg/day may have decreased litter survival (American Cyanamid, 1965) and 9.5-10.5 mg/kg/day decreased pup and litter survival, particularly during the first week after birth (Budreau and Singh, 1973). In addition, short-term studies with

human subjects are available. Volunteers who ingested dimethoate at 0.202 mg/kg/day for 39 days had no obvious toxic effects and no inhibition of blood cholinesterase activity (Edson et al., 1967). These data indicate that 0.202 mg/kg/day is a NOEL for humans. At higher dosages (0.434 mg/kg/day for 57 days, 0.587 mg/kg/day for 45 days and 1.02 mg/kg/day for 14 days), the subjects' blood cholinesterase activities were inhibited, but no symptoms or signs of toxicity were observed. Cholinesterase activities were still decreasing at the end of the test period in each of the groups that received ≥ 0.434 mg/kg/day, indicating that the duration of the experiment was inadequate.

The NOAEL of 2.5 mg/kg/day from the 6- to 12-month dietary study in male rats by Sanderson and Edson (1964) could be used as the basis for an ADI. An uncertainty factor of 100 may be sufficient because of supporting evidence from the 2-year dietary study in rats and mice (NCI, 1977), reproductive studies in mice (American Cyanamid, 1965; Budreau and Singh, 1964) and the short-term studies in humans (Edson et al., 1967) mentioned above. Application of this uncertainty factor results in an ADI of 0.025 mg/kg/day or 1.75 mg/day for a 70 kg man. This ADI is similar to the ADI of 0.02 mg/kg/day derived by the U.S. EPA (1983) and by the World Health Organization (Vettorazzi, 1975) from the human data, using a safety factor of 10 (see Section 7.1.).

Statements concerning available literature in this document refer to published, quotable sources and are not meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies, as well as an unpublished version of the study by Sanderson and Edson (1964), which was used in the above derivation of the ADI. In the unpublished version, brain cholinesterase activity was reported to be markedly inhibited in the rats at 50 ppm, suggesting that this level is the LOAEL rather than a NOAEL; however, one of the study's co-authors indicated that re-evaluation of the data resulted in this response not being presented in the published study (Dourson, 1985).

A close re-examination of all available studies has resulted in a determination that the human NOEL of 0.2 mg/kg bw/day (Edson et al., 1967), supported by a rat NOEL of 0.2 mg/kg bw/day and a LOAEL of 2 mg/kg/day from the Lewerenz et al. (1970) 2-year feeding study, is the most appropriate basis for human ADI derivation. Using an uncertainty factor of 10 for protection of unusually sensitive individuals within the human population, an ADI of 0.02 mg/kg bw/day is calculated. This is the same as the ADI values derived previously by the U.S. EPA (1983) and World Health Organization (Vettorazzi, 1975).

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

Most of these searches were conducted in July, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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